*Leish*MANIA: From pathogens to drug delivery systems

Macrophage-mediated Inflammatory Disorders

Mediators of inflammation induced by macrophages are critical for a variety of human inflammatory disorders (Jou *et al.*, 2013). Our project is on the treatment of joint inflammatory diseases by producing a drug, Interferon beta (INF-β) which is used to the treatment of Rheumatoid Arthritis (RA) with a modelling system based on the Gout.

Leishmania as a new chassis

Nowadays only a few types of chassis are extremely employed and promoted, as bacteria chassis (*Escherichia coli* and *Bacillus subtilis*) and yeast chassis (*Saccharomyces cerevisiae*). Considering this, there are chassis and bioparts intensively used and developed in detriment of others that can provide a foundation for new applications and benefits when considering cells tropism.

The protozoan *Leishmania* is a good new chassis, first because of its ability to infect macrophages (Selvapandiyan *et al*., 2004). Also, because of its ability to express proteins with proper post-translational modifications and its ability to deliver those proteins inside macrophages. The visceral *Leishmania donovani* strain with the virulence factor centrin-1 deleted has very low risks of contamination, and its virulence reduction has been evaluated and confirmed with different animal models, such as mice (Selvapandiyan *et al*., 2006), hamsters (Selvapandiyan *et al*., 2009), and dogs (Fiuza *et al*., 2014). The genetically targeted and defined attenuation reduces the risk of reversal to virulence, a concern generally raised for attenuated organisms that are created by random genomic mutations. *LdCen1* deletion specifically attenuated the amastigote stage of the parasite that replicates inside macrophages, and has no effect on the growth of the promastigote form (Selvapadiyan *et al.*, 2012). In addition, the team is building a Kill Switch system based on the control of the gene of the enzyme 3'nucleotidase/nuclease, which is crucial for the purine rescuing on the promastigote form of the *Leishmania*, the one which is spread by the sandflies, aiming to keep the modified parasite from spreading. The enzyme's synthesis would be regulated by a Tetracycline repressor and so the *Leishmania* would be cultivated in the presence of Tetracycline.

The propose is to use an optimized visceral *Leishmania* strain to direct INF-β to specific macrophages associated to joint inflammatory diseases. The team foresees the possibility of turning this idea into a product.

The struggle

In general, society is detached from academia and new approaches developed in research face initial difficulties in being well accepted by general public. One of the UFMG-Brazil iGEM team project's main challenges is to work with the public acceptance to the use of attenuated pathogens as a disease treatment.

To deal with this issue, the team initially conducted a survey at different points of Belo Horizonte with two main goals: (i) to know how concerned general people would be about the approach proposed by our group; (ii) to inform people about synthetic biology.

Public background and opinion

In order to support the hypothesis of tough acceptance of our project by the general public two surveys would be performed: (i) A quantitative survey (ii) A qualitative survey. Untill the present moment only the quantitative survey was performed. In the survey questions on people's opinions about genetically modified organisms (GMOs), most respondents (75%) showed that they were familiar with the concept, but the majority is unsure about the benefits they can provide (25.7% thinks they are bad for society and 34.2% do not know what to respond) (see Figure attached).

The two main mistrusts reported by the public were the possibility of something going wrong, leading to the creation of a more dangerous pathogen than the pre-existing one; and the lack of faith that the *Leishmania* strain is indeed apathogenic. After a brief explanation on the organism's safety by discussing its disability of causing Leishmaniasis, there was observed an opinion change and people seemed more sympathetic to the idea, leading to a detected 84.5% acceptance to the team's idea, after considering it as a treatment like any other for a disease. The reactions detected in the survey's results made the team realize that there is a lack of information and discussion about genetically modified organisms and synthetic biology between society and scientific community (see figure attached). However, the qualitative survey should be applied in order to understand better why and how interviewees showed a sudden change of opinion after a short explanation on the parasite's safety. Also, the team wishes to investigate how much the interviewees know about safety on GMOs by asking them what kind of expertise would/should be required for the parasite to be safe enough to medical uses.

The resolution

To provide means to increase the exchange of information between general and scientific public, UFMG-Brazil iGEM team created project Ideator. The project comprises a series of actions to disclose synthetic biology to the population and to build a communication channel through which society could pose their questions and demands to the scientific community. It was called Ideator because the team wishes these actions to work as a beginning of the development of a real change in how academy and society relates.

The first action taken was the creation of a subject called "Ideas Incubator", open to the entire University community. Students from several universities can enroll in this subject, even participating remotely via Skype. It was realized that, even among college students, synthetic biology, their implications and potential use were not familiar topics. In the subject, the basis of SynBio, Molecular Biology and general Biochemistry are studied and SynBio application issues (as problems arising from the spread of synthetic biology without specific legislation, and ethical implications) are discussed. The team wishes to offer the subject once a year.

The team is building, through a Facebook page, an ideator pilot project, a place where we can easily reach more people and share more information about synthetic biology's applications for the society. The team will also test what kind of subjects are more accepted by the public before and after the public is informed, and use this data to create more feasible and acceptable synthetic biology projects in the future. The ideator project would go beyond the internet through public interventions in different cities, such as Belo Horizonte, Brasília, São Carlos and São Paulo. These cities have some of the most important Brazilian federal universities which are collaborating with UFMG team. The universities are: Universidade de Brasília (UnB), Universidade de São Paulo (USP), Universidade Federal de São Carlos (UFSCar) and Universidade Federal de São Paulo (UNIFESP). The interventions would not only be used to apply surveys but also to help increase SynBio awareness and to do scientific advertising. Ideas, issues and problems that could be solved using SynBio that the general public may offer will be collected as a way of listening to what the population has to say.

UFMG-Brazil iGEM team is supporting the creation of a community lab in the Federal University of Minas Gerais. The project submitted to funding last year has been recently approved and is beginning to be built. One of the main purposes of a community lab is to create a space to attend demands of the society and put them in practice. To do so, it is necessary to understand how general public feel and think about science and what are their contributions. The team hopes to use this partnership with the community lab not only as a way of spreading science and making it open to everyone, but also, as a way of hearing the population out from a closer relationship.

At last, the team wishes to build the ideator platform at first as a SynBio advertising tool to support the events, subjects and lectures. In the future the team hopes the platform will also work as a data bank for innovation in SynBio, ideas and problems that the population is concerned with as well as suggestions. The platform would be open to everyone as a permanent way of communication between the general public and scientists focusing on what the general public need.

The team believes the combination of these proposals will work as a beginning to a future where the general public and the scientific community in Brazil communicate efficiently and democratically.

References

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Appendage

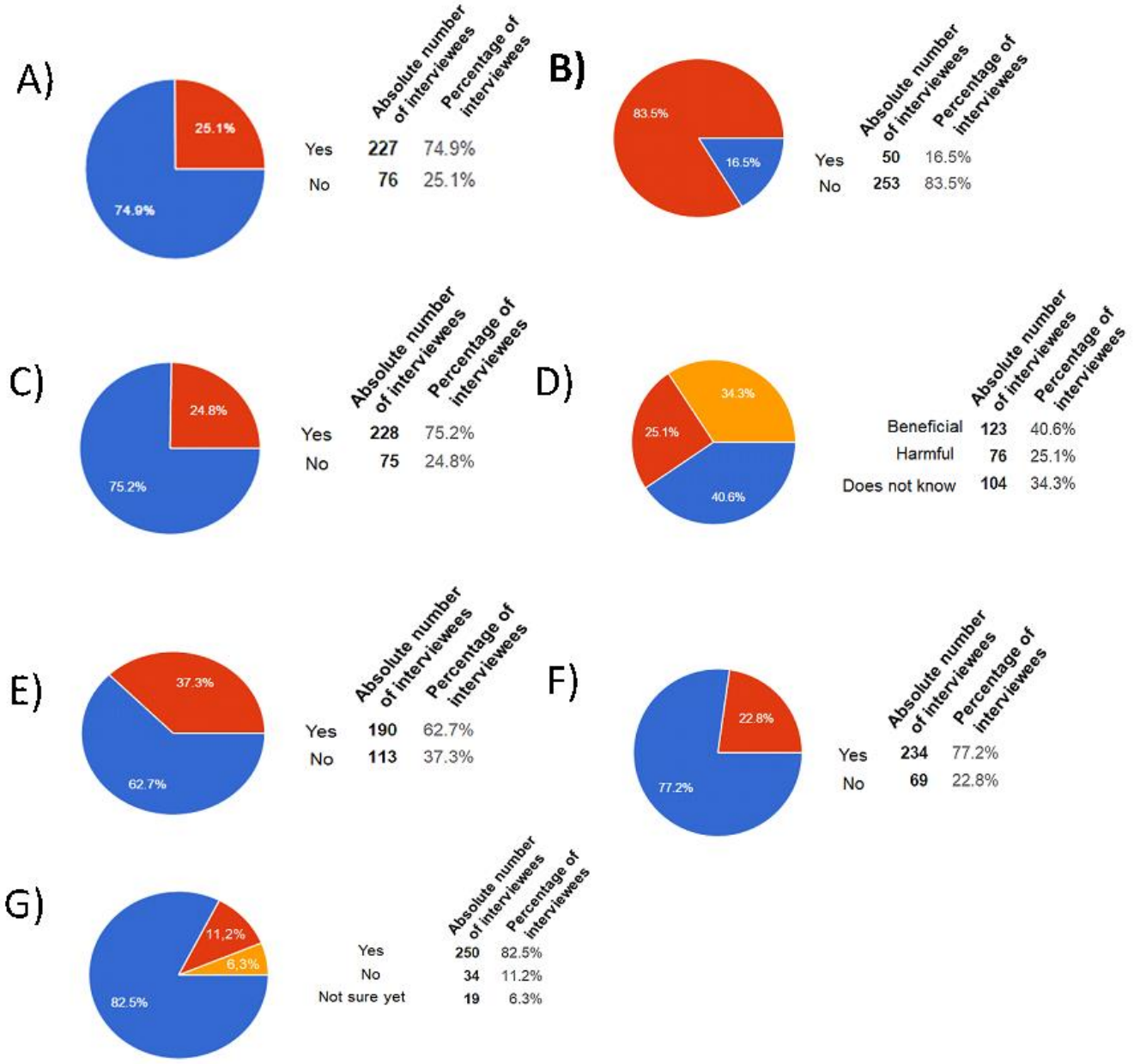

Figure 1. Absolute number and percentage of interviewees for every question. The image A represents the answers to the question “Have you ever heard about *Leishmania*?” The image B represents the answers to the question “Do you think *Leishmania* could be beneficial?” The image C represents the answers to the question “Have you ever heard about GMOs (Genetically Modified Organism)?” The image D represents the answers to the question “Do you believe GMOs to be beneficial or harmful for our society?” The image E represents the answers to the question “Would you accept using modified *Leishmania* as treatment for a disease?” The image F represents the answers to the question “Do you use probiotics, biological baking powder (yeast) or vaccines?” The image G represents the answers to the question ‘‘Given the explanation, would you accept to use *Leishmania* if it was tested and proved safe?”